

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 5 : A61K 47/140, 47/20, 47/40, A01N 25/02</p>		A1	<p>(11) International Publication Number: WO 94/16732 (43) International Publication Date: 4 August 1994 (04.08.94)</p>
<p>(21) International Application Number: PCT/AU94/00023 (22) International Filing Date: 18 January 1994 (18.01.94)</p>		<p>(81) Designated States: AU, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p>	
<p>(30) Priority Data: PL 6862 20 January 1993 (20.01.93) AU</p>		<p>Published <i>With international search report.</i></p>	
<p>(71) Applicants (for all designated States except US): SOLTEC RESEARCH PTY. LTD. [AU/AU]; 8 Macro Court, Rowville, VIC 3178 (AU). GRAMPIAN PHARMACEUTICALS LTD. [GB/GB]; Stag House, Castlebank Street, Glasgow G11 6DY (GB).</p>			
<p>(72) Inventors; and (75) Inventors/Applicants (for US only): HALLS, Neil, Graham [AU/AU]; 8 Marco Court, Rowville, VIC 3178 (AU). KLOSE, John, Barry [AU/AU]; 8 Mosrael Place, Rowville, VIC 3178 (AU).</p>			
<p>(74) Agent: WATERMARK PATENT & TRADEMARK ATTORNEYS; 2nd floor, The Atrium, 290 Burwood Road, Hawthorn, VIC 3122 (AU).</p>			
<p>(54) Title: ECTOPARASITICIDAL FORMULATION</p>			
<p>(57) Abstract</p> <p>This invention relates to a method of treatment of ectoparasitically infested sheep comprising administering to a sheep a pour-on ectoparasiticidal formulation in a volume such that a desired ectoparasite kill rate as hereinbefore defined is achieved. In a second embodiment it also relates to a pour-on formulation effective against ectoparasites of sheep comprising an effective amount of at least one active agent and a non-lanolin dissolving solvent-carrier for said at least one active agent.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

ECTOPARASITICIDAL FORMULATION

Technical Field

This invention relates to formulations active against ectoparasites of animals and particularly to pour-on formulations active against ectoparasites of 5 sheep, as well as to methods of treating such sheep against ectoparasite infestation.

Background Art

Traditionally sheep have been treated against infestation by ectoparasites such as lice or blow fly by dipping the sheep in an 10 ectoparasiticidal formulation so that the animal is totally immersed. The difficulty with this method is that high volumes of the ectoparasiticidal formulation are necessary, that it is difficult to encourage the sheep to enter the dip and that it is both time consuming and physically demanding. A further disadvantage is that 15 large volumes of the "dip" have then to be disposed of in an environmentally correct fashion.

One alternative proposed to dipping animals is to apply an ectoparasiticidal formulation as a "pour-on", the formulation being applied locally, usually along the animal's backline, with the object that, by force of gravity, it spreads around the animal giving protection or treatment to all parts of 20 the animal. One such formulation is disclosed in Australian Patent 563723 to Wellcome Australia Limited. This formulation comprises an anti-parasitic or insecticidal agent suspended or dispersed in an aqueous carrier.

The difficulty with some prior art formulations is that the carrier dries out 25 too quickly and does not allow the active agent to spread across the entirety of the animal's body. Thus untreated areas remain on the animal allowing the infestation to quickly return to the treated parts of the body.

A number of Australian Patents including 77109/81, 61113/90, 599383 and 31919/77 also disclose pour-on formulations. The difficulty with each of these disclosures is, however, that they relate to cattle and not to sheep.

30 It must be appreciated that the fleece of a sheep whether in a shorn or unshorn form presents a unique set of problems in the treatment of ectoparasites; problems which are quite distinct from those of cattle hide. In

particular, in unshorn sheep, the size and bulk of the fleece prevents the formulation being able to reach all parts of the animals body which might be infested, specifically in the brisket and neck region and in the lower parts of the body where infestation is usually high due to the warm, moist environment and

5 its distance from the conventional backline location of application. The size and bulk of a fleece are particularly a problem if organo phosphorus compounds are used as the active agent since these compounds do not readily translocate. For this reason organophosphorus compounds are not commonly used as pour-on ectoparasiticides for sheep.

10 Synthetic pyrethroids are becoming less effective as pour-on ectoparasiticides since the vermin are developing resistance to the common synthetic pyrethroids used.

The consequence of the growing resistance to pour-on formulations against ectoparasiticides based on synthetic pyrethroids is that they are

15 increasingly ineffectual in eliminating infestation of sheep by ectoparasites. Because of the likely reinfestation of the animal subsequent to present treatments their economic benefit is limited. Desirably, such pour-on formulations should be 100% effective against the ectoparasite so that reinfestation is not such a rapid inevitability. The quality of the flock of sheep

20 and thus the economic benefit therefrom can be greatly improved if a 100% kill rate can be achieved.

It is thus an object of this invention to provide a pour-on formulation for treatment of ectoparasites in sheep which achieves a desired kill rate, and preferably a 100% kill rate, by migration around the entirety of the animal's

25 body.

It is a further object of this invention to provide a method of treatment of sheep infested by ectoparasites, which method maximises the probability of migration of the active agent about the entire body surface of the animal.

Summary of the Invention

30 To this end, there is provided a pour-on formulation effective against ectoparasites of sheep comprising an effective amount of at least one active

agent, and a non-lanolin dissolving solvent carrier for said at least one active agent.

This invention is predicated upon the discovery that the reason many ectoparasiticidal formulations do not reach all parts of the animal's body is that

5 they dissolve the lanolin of the sheep's fleece. Thus, on application, they dissolve the lanolin and become "locked" in the fleece preventing their seepage about the animal's body. It has been found that if a solvent-carrier is selected in which lanolin is not dispersible, the translocation of the active agent across the body of either a shorn or unshorn animal is greatly improved.

10 Solvent-carriers which are most suitable for use in the formulations of the invention are those characterized as not being able to dissolve in lanolin at 30°C, and as having a viscosity low enough to enable translocation of the active agent around the body of a sheep to be treated. Desirably the carrier-solvent is also non-toxic. This latter characteristic is important in the treatment of sheep

15 which are to be slaughtered for human consumption.

Throughout this specification, the term "non-lanolin dissolving" is used with respect to solvent-carriers to mean those in which lanolin will not disperse at 30°C.

Several families of solvent-carriers may be suited to the formulation of the

20 invention including vegetable-based esters, co-solvents soluble in both water and oils and low viscosity kerosene-like solvents.

In particular, the more preferred solvent-carriers are those which are vegetable-based esters, phthalates or derivatives thereof.

Examples of suitable phthalates include dibutyl phthalate, di-2-ethylhexyl

25 phthalate, di-iso-octyl phthalate, dimethyl phthalate, diethyl phthalate, di-isobutyl-phthalate, di-isodecyl phthalate or n-octyl n-decyl phthalate.

Other suitable solvent-carriers include glyceryl tricaprylate caprate, peanut oil, sunflower oil, castor oil and PPG-15 stearyl ether.

Active agents which might be incorporated into the formulation of the

30 invention include synthetic pyrethroids, organo phosphorus compounds and insect growth regulators such as Vetrazin™ (cyromazine). Because of the tendency of synthetic pyrethroids to dissolve in the oils released from the

sheeps body after shearing, and because of the increasing resistance to synthetic pyrethroids of ectoparasites to be treated, the more preferred active agents are organo phosphorus compounds, exemplified by diazinon and propetamphos.

5 Preferably, the formulations of the invention are formulated as emulsifiable concentrates. Purely aqueous formulations, it has been found, are less effective.

10 The formulations of the invention may additionally include conventional excipients such as dyes, for example, Macrolex Yellow, Waxoline Yellow, surfactants such as, for example, Alkanate CS, Teric™, Kenmat™, emulsifiers, plasticizers, antioxidants, disinfectants and other conventional formulating agents.

15 In formulations according to the invention, there may be present in the concentrated formulation 20-85% w/w of non-lanolin dissolving solvent-carrier, and 1.0-15.0% w/w of active agent.

In a preferred embodiment of the invention, the concentrate formulation used is as follows:

	%w/w	mass (g)
Diazinon 90S Tech (active agent)	9.878	10.342
Teric 12A4 (surfactant)	1.958	2.050
Corflex 400 (di-butyl phthalate)	68.510	71.730
Alkanate CS (emulsifier)	9.452	9.896
Teric 200 (surfactant)	9.452	9.896
Waxoline Yellow 2GP-FW (dye)	0.750	0.785
TOTAL	100.000	104.699

Diluted 1 volume concentrate plus 6 volumes water as a working solution.

The preferred formulation is as follows.

	%w/w	mass (g)
Diazinon 90S Tech (active agent)	1.468	1.478
Teric 12A4 (surfactant)	0.291	0.292
Corflex 400 (di-butyl phthalate)	10.179	10.247
Alkanate CS (emulsifier)	1.404	1.414
Teric 200 (surfactant)	1.404	1.414
Waxoline Yellow 2GP-FW (dye)	0.111	0.112
Water	85.143	85.743
TOTAL	100.000	100.700

Differences in national regulatory environments mean that different levels of residual sheep ectoparasite infestation are considered acceptable in different countries of the world. Thus, for example, in Australia, in order for a sheep to be

5 acceptably treated, a 100% kill rate must be achieved, i.e. no ectoparasite must remain alive on the treated animal. However, in the United Kingdom, levels lower than 100% are considered acceptable treatment of infestation. "Desired kill rate" when used throughout this specification is thus defined as that of the national regulations of the country concerned.

10 Thus in a second aspect of the invention, there is provided a method of treatment of sheep being ectoparasitically infested comprising administering to a sheep pour-on ectoparasiticidal formulation, such as, for example, that described hereinabove, in a volume such that the desired kill rate is attained.

15 The volume to be applied will vary according to the body surface area to weight ratio of the animal to be treated. For example, in Europe where animals are small in body surface area but nevertheless weighty, the preferred volume to be applied is one that is greater than 1.0 ml per kilo bodyweight of the sheep to be treated. In Australia, however, where sheep are larger in body surface area but no weightier than European sheep, the desired volume is one that is

20 greater than 2.0 ml per kilo body weight of the sheep to be treated.

This aspect of the invention is predicated on the discovery that reinestation of sheep currently occurs basically as a result of untreated ectoparasites remaining in the brisket and remote regions of the animal. By

increasing the volume of application (but not necessarily the concentration of active) it has been found that there is a stronger likelihood that the desired kill rate will be attained because the remote regions of the sheep are also treated.

It will be appreciated that the upper limit of volume of emulsion applied 5 will vary depending on the state of the fleece of the sheep. A heavily fleeced sheep will require a larger quantity of emulsion than a shorn sheep.

It will also be appreciated that excess volumes applied will only result in substantial run-off and hence wastage, and thus should be avoided.

Wherein the desired kill rate is defined by national regulation laws, in a 10 preferred embodiment of the invention there is provided a method of treatment of sheep being ectoparasitically infested comprising administering to a sheep a pour-on ectoparasiticidal formulation such as, for example, that described hereinabove, wherein the active agent is present in an amount such that when delivered in the desired formulation volume, the desired kill rate is attained. The 15 concentration will vary with active and the resistance of the ectoparasite to be treated.

For example, where the active agent is Diazinon, an organo phosphorus compound, the desired rate of application of the ectoparasiticidal formulation is about 40 mg/kg active agent delivered in a volume of about 3 ml per kilo body 20 weight of the infested sheep. It will be appreciated that the necessary concentration of active will vary depending on its chemical nature. In the case of Propetamphos, the desired concentration is one which is greater than 15 mg/kg.

The longer an animal remains infested with ectoparasites, the more likely 25 its fleece will be damaged due to the tendency of the animal to rub against objects to relieve irritation caused by infestation. It is thus desirable to eradicate infestation in as rapid a period as possible.

Thus in a third aspect of the invention, there is provided a method of treatment of sheep being ectoparasitically infested comprising administering to 30 a sheep a pour-on formulation, such as, for example, that described hereinabove in a volume such that the desired kill rate, as defined hereinabove,

is substantially achieved within 14 days after treatment. Preferably the volume applied is greater than 2.0 ml per kilo body weight of the sheep to be treated.

The formulations according to the invention can be applied to long-wooled (fully fleeced) or shorn sheep although it will be appreciated that since 5 the formulation acts upon the skin of the sheep, to deliver the formulation to a fully fleeced sheep will require a considerable excess to allow for uptake of the formulation by the fleece itself.

Further embodiments of the invention will now be described by way of example. The invention should not, however, be considered as being limited 10 thereto.

Calculations are based on the assumption that sheep are used having an average weight of approximately 50 kg and "success" is designated as a kill rate of 100% given that all tests were carried out under Australian and New Zealand conditions.

15 Testing for ectoparasite infestation was carried out by counting the number of parasites present in 20 partings taken on each side of the sheep (40 partings in total).

EXAMPLE 1 - POUR-ON LOUSICIDE EFFICIENCY AGAINST DAMALINIA OVIS

20 **EXAMPLE 1A:** An emulsion was formulated according to the following:

Ingredient	% w/w	mass (g)
Diazinon (90.0%)	2.325	23.25
Teric 12A4	0.50	5.0
Macrolex Yellow 3G	0.10	1.0
Corflex 440 (di-isobutyl phthalate)	16.975	169.75
Alkanate CS	2.5	25.0
Teric 200	2.5	25.0
BHA	0.1	1.0
DI water	74.86	748.6
Nipastat	0.14	1.4
	100.0	1000.0

The pour-on emulsion (Diazinon 2.1% w/w) was applied in a volume of 1.67 ml/kg body weight as a band commencing high on the neck of the sheep and finishing at the butt of the tail. Further bands were applied to either side of the initial stripe and partially overlapping the first until the appropriate volume was 5 delivered. The treatment was applied immediately after shearing as follows:

Ear Tag No	Weight (kg)	Dose Vol (mls)	Dose (mg/kg)
232	27	45	35
177	25	40	33.6
212	33	55	35
187	33	55	35
203	30	50	35
208	25		Untreated Controls
181	27		Untreated Controls
241	32		Untreated Controls
246	21		Untreated Controls
219	30		Untreated Controls

Treatments were administered using the Protector - dial a dose, drench/pour-on gun.

Once treated, each group was penned separately in an electrified 10 paddock where they were kept for the duration of the trial.

Lice counts were performed pre-shearing, 7, 14, 21, 28, 35 and 42 days after treatment, using the 20 partings per side technique.

Results were calculated from the mean number of lice in each group. Percentage reduction of the lice count in the lice group was used as a 15 correction factor.

The formula used was as follows

$$\% \text{ reduction} = 100 \times (1 - T_2/C_2 \times C_1/T_1)$$

Where T_1 = pre treatment lice count of the treated group

T_2 = post-treatment lice count of the treated group

C_1 = pre-treatment lice count of the control group

C_2 = post-treatment lice count of the control group

Group	Pre Shear	7 DAT	14 DAT	21 DAT	28 DAT	35 DAT	42 DAT
Treated sheep	362.8	31.2	3.2	0.2	0.2	0.4	0
Control	353.4	306.2	311	244	196	200.8	166.4
% Reduction	-	90	99	99.9	99.9	99.8	100

Eradication of the sheep body louse *D. ovis* was achieved at a kill rate of
5 100% after 42 days of treatment using the formulation of this example.

EXAMPLE 1B: To demonstrate the activity of active ingredients other than Diazinon, a formulation according to the following was prepared:

Ingredient	% w/w	mass (g)
Teric 12A4	1.958	78.32
Waxoline Yellow 2GP-FW	0.375	15.00
Corflex 400	73.824	2952.96
Alkanate CS	9.452	378.08
Teric 200	9.452	378.08
Propetamphos (90-91% w/w)	4.939	197.56
	100.000	4000.00

10 The pour-on emulsion (diluted 1:6) was applied in a volume of 3 ml/kg body weight in a manner similar to that described in Example 1A in a concentration of 20 mg/kg.

Lice counts were performed pre-shearing 7, 14, 21, 28, 35 and 42 days after treatment using the 20 partings per side technique.

15 Using the calculation methods described in Example 1A the following results were achieved:

Group	Pre Shear	7 DAT	14 DAT	21 DAT	28 DAT	35 DAT	42 DAT
Control	444.2	365.2	324.8	227.4	193.8	178.4	130.6
Treated sheep	435.8	0.8	0	0	0	0	0
% Reduction	-	99.8	100	100	100	100	100

Eradication of the sheep body louse *D. ovis* was achieved at a kill rate of 100% after only 14 days of treatment using the formulation of this example.

COMPARISON EXAMPLE 1 - EXCLUSION OF PHTHALATE EXTENDER

5 As a point of comparison with the formulations described in Example 1, a formulation excluding the phthalate extender Corflex 440 (di-isobutyl phthalate) and in the absence of any other substitute extender, was prepared as follows:

Ingredient	% w/w	mass (g)
Diazinon (91%)	1.48	14.8
Teric 12A4	0.29	2.9
Macrolex Yellow 3G	0.11	1.1
Alkanate CS	1.40	14.0
Teric 200	1.40	14.0
Water	95.27	952.7
Orthophenylphenol	0.05	0.5
	100.00	1000.0

The formulation was applied immediately after shearing in a manner as 10 described in Example 1 and in a volume of 150 ml/50 kg sheep.

Percentage reduction was calculated as in previous examples.

Group Lice Counts

Ear Tag No	Pre Shearing	7 DAT	14 DAT	21 DAT	28 DAT	35 DAT	42 DAT
231	742	126	DIED				
43	365	286	110	39	20	21	3
41	347	253	135	51	26	17	7
52	298	125	41	5	3	3	7
97	260	205	104	90	70	104	50
Average	402.4	199	97.5	47.7	29.8	36.3	16.8
Kill rate		41.0%	73%	87.0%	91.2%	88%	94%
<u>CONTROLS</u>							
31	730	618	605	570	607	445	483
24	390	309	304	275	300	135	72
143	466	477	429	364	329	465	396
13	268	102	215	273	247	274	233
156	249	236	285	301	284	195	245
Average	420.6	348.4	367.6	396.6	353.4	302.8	284.6

It is clear that a satisfactory sustained kill rate was not achieved in the absence of a phthalate extender.

5 COMPARISON EXAMPLE 2 - SUBSTITUTION OF PHTHALATE EXTENDER BY ALTERNATIVE EXTENDER IN WHICH LANOLIN IS SOLUBLE

As a further point of comparison with the formulation described in Example 1 and to show the efficacy of an extender not soluble in lanolin, the following formulation was prepared:

12

<u>Ingredient</u>	<u>% w/w</u>	<u>mass (g)</u>
Diazinon (90.0%)	12.0	84.0
Teric 12A4	2.1	14.7
Macrolex Yellow 3G	0.8	5.6
Solvesso 150 (extender)	65.1	455.7
Alkanate CS	10.0	70.0
Teric 200	10.0	70.0
	<u>100.0</u>	<u>700.0</u>
	<u> </u>	<u> </u>

The formulation was emulsified in a concentrate:water ratio of 1:3 such that the active was present in a concentration of 2.7% w/w.

(Diazinon pour on concentrate 10.8% w/w)

5 The emulsion was applied in a volume of 1.67 mL/kg body weight at the same time and in the same manner as described in Example 1, according to the following:

Ear Tag No	Weight (kg)	Dose Vol (mL)	Dose (mg/kg)
Y51	36	60	45.0
Y59	48	80	45.0
Y57	52	85	44.1
Y52	35	60	46.3
Y55	42	70	45.0
Y53	40	Untreated Controls	
Y54	39	"	"
Y60	46	"	"
Y58	37	"	"
Y56	41	"	"

Treatments were administered using the Protector dial a dose drench/pour-on gun.

Once treated, each group was penned separately in an electrified paddock where they were kept for the duration of the trial.

5 Lice counts were performed pre-shearing 7, 14, 21, 28, 35 and 41 days after treatment using the 20 partings per side technique.

The formula used was as follows

$$\% \text{ reduction} = 100 (1 - T_2/C_2 \times C_1/T_1)$$

Where T_1 = pre treatment lice count of the treated group
 10 T_2 = post-treatment lice count of the treated group
 C_1 = pre-treatment lice count of the control group
 C_2 = post-treatment lice count of the control group

Group	Pre	7 DAT	14 DAT	21 DAT	28 DAT	35 DAT	41 DAT
Shear							
Treated sheep	286.0	154.8	50.8	21.4	21.2	7.8	8.0
Control	281.4	250.4	245.0	227.0	189.2	196.8	157.4
% Reduction	-	51.8	79.6	90.7	89.0	96.1	95.0

15 In the absence of a phthalate extender, using a conventional solvent - extender, Solvesso 150, as a replacement therefor, eradication of D. ovis to a degree sufficient for Australian Standards was not achieved.

EXAMPLE 2 - INCREASED VOLUME OF APPLICATION

To test whether or not increased volume of application achieved a faster kill rate, an aqueous emulsion of Diazinon was prepared according to the 20 following:

<u>Ingredient</u>	<u>% w/w</u>	<u>mass (g)</u>
Diazinon (910 g/kg)	1.67	25.05
Teric 12A4	0.29	4.35
Macrolex Yellow 3G	0.11	1.65
Corflex 440	9.0	135.0
Alkanate CS	1.4	21.0
Teric 200	1.4	21.0
Water	86.13	1291.95
	100.00	1500.00

This formulation was applied in a volume of 3mL/kg body weight of animal, the Diazinon being present in a concentration of 1.5% w/w, the dose rate being approximately 45 mg/kg.

5 All sheep were treated in the same manner as described in Example 1 and immediately post-shearing.

Ear Tag No	Treatment	Weight (kg)	DoseVol (mL)	Dose (mg/kg)
90	Test formulation	45	135	45.0
244	"	50	150	45.0
281	"	49	150	45.9
148	"	47	140	44.7
1	"	47	140	44.7
61	Control	46	-	-
46	"	46	-	-
84	"	41	-	-
88	"	43	-	-
12	"	41	-	-

Treatments were applied using the NZ Protector dial-a-dose drench/pour-on gun.

10 Once treated, each group was penned separately in electrified paddocks where they remained for the duration of the trial.

Lice counts were performed pre-shearing 7, 14, 21, 29, 35, 42, 49 and 57 dat using the 20 partings per side technique.

15

Percentage reduction in lice counts was calculated using the change in lice counts for the control group as a correction factor.

The formula used to calculate % reduction was the same as that used in Example 1, with the following result:

5 Mean Lice Counts - Days after Treatment (DAT)

Pre-Shear	7 DAT	14 DAT	21 DAT	29 DAT	35 DAT	42 DAT	49 DAT	57 DAT
Treated sheep	193.2	0.2	0	0	0	0	0.2	0
Control	185.0	100.8	72.0	50.4	58.8	56.6	52.6	48.4
% Red'n	-	99.8	100.0	100.0	100.0	100.0	99.6	100.0

Eradication of the sheep body louse D. ovis was achieved after 14 days showing that increased volume of application gives more expedient results.

EXAMPLE 3 - VARYING CONCENTRATION OF ACTIVE

10 In order to determine the minimum effective concentration of active agent possible upon application of 150 mL/50 kg sheep, the following formulations were prepared:

Base formulation

Ingredient	% w/w	mass (g)
Diazinon (91%) }	87.8	526.0
Water		
Macrolex Yellow 3G	0.11	
Corflex 440	9.00	5.0
Alkanate CS	1.40	8.0
Teric 200	1.40	84.0
Teric 12A4	0.29	17.4
	100.0	6000.0

16

<u>Example 3A</u>		(40 mg/kg)	(1.33% Diazinon w/w)
	base formulation	12.2	122.0
	Diazinon (91%)	1.47	14.7
	water	86.33	863.3
		_____	_____
5		100.0	1000.0
 <u>Example 3B</u>		(35 mg/kg)	(1.16% Diazinon w/w)
	base formulation	12.2	122.0
	Diazinon (91%)	1.28	12.8
	water	86.52	865.2
		_____	_____
10		100.0	1000.0
 <u>Example 3C</u>		(30 mg/kg)	(1.0% Diazinon w/w)
	base formulation	12.2	122.0
	Diazinon (91%)	1.10	11.0
	water	86.70	867.0
		_____	_____
15		100.0	1000.0
 <u>Example 3D</u>		(25 mg/kg)	(0.83% Diazinon w/w)
	base formulation	12.2	122.0
	Diazinon (91%)	0.92	9.2
	water	86.88	868.8
		_____	_____
20		100.0	1000.0
 <u>Example 3E</u>		(20 mg/kg)	(0.66% Diazinon w/w)
	base formulation	12.2	122.0
	Diazinon (91%)	0.73	7.3
	water	87.07	870.7
		_____	_____
25		100.0	1000.0

For each of Examples 3A-E, the treatments were applied immediately after shearing along the backline in 4-6 strips (depending on the volume to be applied. Details are as follows:

Ear Tag No	Treatment	Weight (kg)	Dose Vol (mL)	Dose (mg/kg)
160	Example 3A	40	120	40
171	"	49	150	40
196	"	44	130	40
124	"	51	155	40
139	"	43	130	40
170	Example 3B	47	140	35
197	"	45	135	35
271	"	43	130	35
66	"	43	130	35
135	"	42	125	35
98	Example 3C	43	130	30
119	"	43	130	30
228	"	48	145	30
69	"	47	140	30
63	"	47	140	30
155	Example 3D	43	130	25
237	"	52	155	25
136	"	44	130	25
283	"	42	125	25
193	"	44	130	25
191	Example 3E	45	135	20
198	"	42	125	20
187	"	42	125	20
105	"	48	145	20
175	"	41	125	20
82	Control	44	-	-
149	"	49	-	-
161	"	52	-	-
166	"	47	-	-
85	"	42	-	-

Treatments were applied using the NZ Protector dial-a-dose drench/pour-on gun.

Once treated, each group was penned separately in electrified paddocks where they were kept for the duration of the trial.

5 Lice counts were performed pre-shearing 7, 14, 21, 28, 35 and 42 days after treatment using the 20 partings per side technique.

Percentage reduction in lice counts was calculated using the change in lice counts for the control group as a correction factor, using the formula given in example 1.

10 Mean Lice Counts - Days After Treatment (DAT)

	Pre-Shear	7 DAT	14 DAT	20 DAT	28 DAT	35 DAT	42 DAT
Example 3A							
Treated Sheep	163.8	42.4	19.6	6.4	3.4	2.6	0
Control	141.2	66.8	112.8	92.6	73.8	81.8	58.8
% Red'n		45.3	85.1	94.1	96.0	97.3	100.0
Example 3B							
Treated Sheep	161.2	1.2	0.4	0	0	0	0
Control	141.2	66.8	112.8	92.6	73.8	81.8	58.8
% Red'n		98.4	99.7	100.0	100.0	100.0	100.0
Example 3C							
Treated Sheep	150.8	14.6	2.4	0.8	0.8	0.6	0
Control	141.2	66.8	112.8	92.6	73.8	81.8	58.8
% Red'n		79.6	98.0	99.2	98.9	99.3	100.0
Example 3D							
Treated Sheep	143.8	212.8	7.6	0.2	3.2	3.8	1.8
Control	141.2	66.8	112.8	92.6	73.8	81.8	58.8
% Red'n		66.6	93.4	99.8	95.8	95.5	97.1
Example 3E							
Treated Sheep	140.2	5.2	1.2	0.2	0	0	0.2
Control	141.2	66.8	112.8	92.6	73.8	81.8	58.8
% Red'n		92.2	98.9	99.8	100.0	100.0	99.7

Eradication of sheep body louse was achieved at 42 days using formulations 3A, 3B and 3C. Thus it is clear that these formulations are effective in achieving 100% kill rate, although higher concentrations are likely to give more expedient results, i.e. 100% kill in a lesser period of time.

5 In the Example 3A group, one animal was responsible for the delay in achieving 100% efficacy. The counts at 7, 14, 21, 28, 35 and 42 days post-treatment were 185, 94, 31, 17, 13 and 0 respectively. This sheep was extremely heavily infested and was difficult to shear; i.e. tufts of wool were present at treatment.

10 Similar tests using concentrations of Diazinon firstly at 15 mg/kg (0.5% w/w) and secondly at 10 mg/kg (0.33% w/w) failed to eradicate the sheep body louse D. ovis.

EXAMPLE 4 - COMPARISON OF PHTHALATE EXTENDERS

To show that phthalate extenders other than di-isobutyl phthalate are effective for the purposes of the invention, the following formulations were prepared:

EXAMPLE 4A

Ingredient	% w/w	mass (g)
Diazinon (91%)	1.47	16.17
Teric 12A4	0.29	3.19
Macrolex Yellow 3G	0.11	1.21
Corflex 400 (di-butyl phthalate)	9.00	9.0
Alkanate CS	1.40	1.54
Teric 200	1.40	14.0
Deionised Water	86.28	949.08
Orthophenylphenol	0.05	0.55
	100.00	1100.0

(1.33% Diazinon w/w; dose = 3.0 mL/kg ≈ 40 mg/kg)

EXAMPLE 4B

Ingredient	% w/w	mass (g)
Diazinon (91%)	1.47	16.17
Teric 12A4	0.29	3.19
Macrolex Yellow 3G	0.11	1.21
DIBP (di-isobutyl phthalate)	9.00	99.00
Alkanate CS	1.40	15.40
Teric 200	1.40	15.40
Deionised Water	86.28	949.08
Orthophenylphenol	0.05	0.55
	100.0	1100.0
	—	—

(1.33% Diazinon w/w; dose = 3.0 mL/kg ≈ 40 mg/kg)

All sheep were treated immediately after shearing according to the
5 manner described in Example 1. No control group was used.

Ear Tag No	Treatment	Weight (kg)	Dose Vol (mL)	Dose (mg/kg)
263	Example 4A	27	80	39.4
201	"	39	115	39.2
279	"	33	100	40.3
95	"	37	110	39.5
61	"	41	125	40.6
227	Example 4B	34	100	39.1
242	"	30	90	39.9
205	"	34	100	39.1
125	"	34	100	39.1
46	"	40	120	39.9

Treatments were applied using the NZ Protector dial-a-dose drench pour-on gun.

Once treated, each group was penned separately under cover for 9 days,
10 after which they were penned outside in electrified paddocks where they were
kept for the duration of the trial.

Lice counts were performed pre-shearing, 7, 14, 21, 28, 35 and 43 DAT using the 20 partings per side technique.

Percentage lice reductions were calculated by dividing the average pre-shearing lice count into the average weekly lice count for that group.

5 Group Mean Lice Counts

Pre-Shear	7 DAT	14 DAT	21 DAT	28 DAT	35 DAT	43 DAT
Example 4A						
Treated Sheep 353.6	27.0	6.8	3.0	1.60	0.2	0
% Red'n	92.0	98.0	99.0	99.5	99.9	100
Example 4B						
Treated Sheep 348.6	14.2	4.6	0	0	0	0.2
% Red'n	95.9	98.6	100	100	100	99.9

It is evident from these results that the formulations of Examples 4A and 4B are equivalent showing that dibutyl phthalate is an acceptable substitute for di-isobutyl phthalate.

10 EXAMPLE 5 - FIELD TESTS

To determine large scale efficacy of formulations according to the invention a formulation was prepared as follows:

Ingredient	% w/w	mass (g)
Diazinon 90S (Technical) (90.5%)	9.878	29.634
Teric 12A4	1.958	5.874
Macrolex Yellow 3G	0.743	2.229
Corflex 400 (dibutyl phthalate)	68.517	205.551
Kemmat SC15	9.452	28.356
Teric 200	9.452	28.356
	100.000	300.000
	_____	_____

(diluted to 1 vol. conc.: 6 vol water to give Diazinon 1.33% w/w)

Formulation was applied to sheep using a Magrath electric hand wand using 10 cm perforated brass "T" piece screw on nozzle.

A total of 901 sheep were treated immediately off shears as follows:

Prior to shearing, 25 2½ - 5½ year old merino ewes were randomly selected, ear tagged and counted for lice. A post-shearing lice count was then conducted.

The sheep were then weighed and dosed immediately after shearing according to the weight of the heaviest sheep in each mob i.e.,

BODY WEIGHT - KG	DOSE VOLUME - mL
0-30	90
31-40	120
41-50	150
51-60	180
61-70	210
71-75	225

10 Sheep in excess of 75 kg body weight to be dosed at 3.0 mL per kg live weight.

The appropriate dose was applied to the backline of each sheep in the mob in a single unbroken band approximately 120 mm wide, extending from behind the ears through to the butt of the tail.

15 TABLE 1

MOB	NO. TREATED	HEAVIEST B/W RECORDED (Shorn) (kg)	DOSE VOL (mL)
Weaners	159	47	150
1½ y/o ewes	113	55	180
2½ - 5½ y/o ewes	601	57	180
2½ y/o wethers	28	65	210

Lice counts were performed using the 20 partings per side technique as follows:

Pre-shearing	25 eartag sheep				
Post-shearing	25 eartag sheep				
34 DAT	25 eartag sheep	+ 25 others at random*			
85 DAT	25 eartag sheep	+ 25 others at random*			
134 DAT	25 eartag sheep	+ 25 others at random*			
190 DAT	25 eartag sheep	+ 25 others at random*			

* Any sheep showing signs of rubbing are to be included in this group of 25:
The average number of lice found per sheep in each group was as follows:

TABLE 2

	Pre-Shear	Post-Shear	34 DAT	85 DAT	134 DAT	190 DAT
25 Eartag sheep	146.6	71.7	0	0	0	0
25 Others			0	0	0	0

Evidently eradication of D. ovis was achieved using the formulation of this example. No lice were found at subsequent inspections.

EXAMPLE 6 - DEGREE OF TRANSLOCATION

15 To determine the degree and speed of translocation of the formulation of the invention over the body surface of a sheep after treatment, the following formulation was prepared and administered:

	%w/w	mass (g)
Diazinon 90S Tech	9.878	3.75
Teric 12A4	1.958	0.74
Corflex 400	68.510	26.04
Kenmat	9.452	3.59
Teric 200	9.452	3.59
Waxoline Yellow 2GP-FW	0.750	0.29
	100.000	38.00

(diluted 1:6 by volume to give Diazinon 1.33% w/w)

A 3 year old merino was shorn, weighed and treated immediately with the diazinon spray-on. It had not received any insecticide treatment for 12 months. The sheep weighed 37 kg and was treated with 110mL of the product. A wide band was applied from high on the neck, behind the ears, to the butt of the tail at 5 a dosage rate of 3mL per kg bodyweight.

The animal was hand restrained during treatment and placed under cover in a pen with mesh floor and sides for the duration of the trial.

During and after treatment, the sheep had no contact with other treated animals and was not exposed to any rain.

10 On advice from the State Chemistry Laboratory, Department of Agriculture, Victoria, approximately 2cm square scrapings of wool and skin were taken as follows:

<u>DAY 0</u> <u>& DAYS 1.3.7</u>	15 minutes after treatment 2 samples, left and right in the middle of the back and in the band of product.
<u>DAY 1.3.7</u>	Mid-line - half way from the backline to the bellyline, at the line of the shoulder, mid-flank and rump ie., 6 samples at each time period. This was repeated on the other side of the body ie., 12 samples in total.
<u>DAY 1.3.7</u>	Bellyline - at the line of the shoulder, mid-flank and rump on both sides ie., 12 samples at each time period.
<u>DAY 1.3.7</u>	A scraping was taken from the neck/brisket area, in the mid-line - see above diagram. Care was taken in positioning the scrapings eg., left bellyline shoulder sample was exactly vertically below the mid-line shoulder sample at day 1, so that samples at days 3 and 7 were minimally affected by variations in diazinon spread caused by bare patches above the lower samples at days 3 and 7. A new scalpel blade was used for each scraping site.

Tables 3, 4 and 5 show the levels of diazinon detected at each test point throughout the trial.

Table 3 - DIAZINON (PPM) - WHOLE WOOL

DAYS POST TREATMENT	BACKLINE		MID-LINE LEFT		
	LEFT	RIGHT	SHOULDER	FLANK	RUMP
0	21,000	16,000			
1	19,000	19,000	1400	84	940
3	15,000	16,000	1100	220	170
7	21,000	17,000	730	190	590

DAYS POST TREATMENT	MID-LINE RIGHT			BELLY-LINE LEFT		
	SHOULDER	FLANK	RUMP	SHOULDER	FLANK	RUMP
0						
1	290	230	470	180	150	890
3	320	170	480	140	360	54
7	210	110	390	290	150	420

DAYS POST TREATMENT	BELLY-LINE RIGHT			NECK	
	SHOULDER	FLANK	RUMP		
0					
1	430	87	53	230	
3	210	54	73	220	
7	530	52	65	170	

Table 4 - DIAZINON (PPM) - WHOLE WOOL

DAYS POST TREATMENT	MIDLINe		BELLY-LINE	
	MEAN	RANGE	MEAN	RANGE
1	569	84-1400	298	53-890
3	410	170-1100	148.5	54-360
7	370	110-730	251.2	52-530

Table 5 - DIAZINON (PPM) - WHOLE WOOL (MEAN VALUES)

DAYS POST TREATMENT	MIDLINe		BELLY-LINE	
	LEFT	RIGHT	LEFT	RIGHT
1	808	330	407	190
3	496	323	185	112
7	503	237	287	216

The values (PPM diazinon) are reported on a whole wool basis.

The laboratory determined the percentage wool grease on 3 samples - 16.11%, 21.5% and 17.6% w/w.

The approximate concentration in wool grease can be calculated on the 5 basis of the average wool grease content of the wool is 18.4% w/w ie., multiply the individual results by a factor of 5.4.

Due to difficulties in handling the trial animal, the band applied did deviate somewhat to the left side of the mid-line. However, this would be seen in a commercial situation on some sheep and highlights the worth of a wide 10 band of product being applied. The levels detected on the right belly-line at the flank and rump levels for days 1, 3 and 7 demonstrate the effect of the deviation of the band to the left. However, there was still ample coverage of this right side eg., Day 1, "belly-line right rump" 53 PPM diazinon in whole wool, or 286 PPM in the wool grease and presumably the skin fats and oils, where the lice live and 15 breed.

Particular note is made of the fact that levels detected in the neck/brisket region at all stages was high illustrating the ability of the formulation to translocate across the entire animal.

A wide variation in the range of diazinon levels is noted; translocation 20 would be affected by length of wool after shearing, conditions of the skin, wool follicle density, wool and skin grease levels and the level applied at the back-line. At day 7, this range had tightened considerably.

EXAMPLE 7 - LONG-WOOLLED SHEEP

The following trials conducted in New Zealand demonstrate that the 25 formulations according to the invention may also be useful against ectoparasite infestation of long-woolled sheep.

The following formulation was prepared and administered to Romney/Border Leicester ewes having 10-12 cm of wool growth.

	%w/w	mass (kg)
Diazinon 90S Technical	9.878	29.634
Teric 12A4	1.958	5.874
Macro-lex Yellow 3G	0.743	2.229
Corflex 400	68.517	205.551
Kenmat SC15	9.452	28.356
Teric 200	9.452	28.356
TOTAL	100.000	300.700

(diluted 1:6 by volume to give Diazinon 1.33% w/w : rate = 3ml/kg)

The ewes were sprayed along the backline using a Protector gun and narrow nozzle. The treatment extended from the base of the neck to the rump in 5 a 15 cm wide band.

The following results were achieved when a procedure of counting the lice in a 10 cm parting of wool at 10 sites around the body (being the brisket, neck, lower and upper shoulders and withers on each side of the body) was adopted.

Ear Tag No.	Weight (kg)	Dose Vol (mls)	Louse Scores		
			D.A.T.	0	21
370	67	201	9	3	0
371	80	240	11	0	0
372	78	234	11	1	0
373	53	165	17	DEAD	
374	73	219	13	0	0
375	73	219	7	0	0
497	67	201	62	1	0
498	78	234	35	0	0
499	85	255	21	0	0
500	80	240	45	1	0

Thus a 97.4% reduction was achieved 21 days post-treatment and 100% reduction was achieved 41 days post-treatment.

EXAMPLE 8 - RAIN AFFECTED TREATMENT

A further advantage of the formulations according to the invention is that 5 they appear to be unaffected by post-treatment rain.

The following example illustrates the efficacy of a formulation according to the invention applied to sheep 4 hours prior to heavy rain.

The following formulation was prepared and administered to romney sheep having 2.5-4.0 cm wool growth.

	%w/w	mass (kg)
Diazinon 90S Technical (9051)	9.878	29.634
Teric 12A4	1.958	5.874
Macro-lex Yellow 3G	0.743	2.229
Corflex 400	68.517	205.551
Kenmat SC15	9.452	28.356
TOTAL	100.000	300.700

(diluted 1:5 : application rate 3ml/kg, 45 mg/kg)

Results achieved were as follows:

Group	% reduction in lice numbers weeks post-treatment					
	1	2	3	4	5	6
Treated sheep	100	100	100	100	100	100
Control	15.5	15.4	41.5	65.3	28.0	41.5

Thus, despite heavy rain post-treatment, formulations according to the 15 invention were effective in eradicating lice infestations. In such weather conditions, sheep are not usually re-treated and this can result in failure to eradicate lice.

It is evident from the above that inclusion of a phthalate extender in pour-on formulations based on organo phosphorus compounds gives substantial

advantages over prior art formulations used to treat ectoparasiticidal infestation in sheep.

Furthermore, it is evident that application of such formulations in volumes greater than 2.0 mL/kg body weight of animal also achieves substantially 5 improved effects over prior art formulations designed to ectoparasitically treat sheep.

Whilst this invention has been described with respect to Damalinia Ovis; sheep lice, it may also be active against other ectoparasites such as blowfly. Thus the invention should be seen as being not restricted to the particular 10 ectoparasites upon which trials have been conducted.

It will be understood that this invention is not limited to the specific embodiments described herein but that substitutions particularly of chemical alternatives may be carried out whilst the core of the invention remains the same.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treatment of ectoparasitically infested sheep comprising administering to a sheep a pour-on ectoparasiticidal formulation in a volume such that a desired ectoparasite kill rate as hereinbefore defined is achieved.
2. A method according to claim 1 wherein the volume of ectoparasiticidal formulation administered is greater than 1.0 ml per kilo bodyweight of a sheep to be treated.
3. A method according to one of claims 1 or 2 wherein the volume of ectoparasiticidal formulation administered is greater than 2.0 ml per kilo bodyweight of a sheep to be treated.
4. A method according to any one of claims 1 to 3 wherein the desired ectoparasite kill rate is 100%.
5. A pour-on formulation effective against ectoparasites of sheep comprising an effective amount of at least one active agent and a non-lanolin dissolving solvent-carrier for said at least one active agent.
6. A pour-on formulation as claimed in claim 5 wherein said active agent and said non-lanolin dissolving solvent-carrier are present in amounts such that the formulation is effective against ectoparasites when delivered in a volume of greater than 1.0 ml per kilo bodyweight of a sheep to be treated.
7. A pour-on formulation as claimed in claims 5 or 6 wherein said non-lanolin dissolving solvent-carrier is selected from the group consisting of vegetable based esters, phthalates, co-solvents soluble in both water and oils and low viscosity kerosene-like solvents.

8. A pour-on formulation as claimed in any one of claims 5-7 wherein said non-lanolin dissolving solvent-carrier is a phthalate.
9. A pour-on formulation as claimed in any one of claims 5-8 wherein said active agent is present in an amount of 1-15% w/w and said non-lanolin dissolving solvent-carrier is present in an amount of 20-85% w/w.
10. A pour-on formulation as claimed in any one of claims 5-9 wherein said active agent is an organophosphorous compound.
11. A method of treatment of ectoparasitically infested sheep comprising administering to a sheep a pour-on ectoparasiticidal formulation comprising an organophosphorus active agent and a non-lanolin dissolving solvent carrier.
12. A method according to claim 11 wherein said non-lanolin dissolving solvent-carrier is selected from the group consisting of vegetable based esters, phthalates, co-solvents soluble in both water and oils and low viscosity kerosene-like solvents.
13. A method according to claims 11 or 12 wherein said non-lanolin dissolving solvent-carrier is a phthalate.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 94/00023

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.⁵ A61K 47/140, 47/20, 47/40, A01N 25/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC A61K 47/00, 47/140, 47/40, 47/20, 9/08, 9/10, A01N 25/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as aboveElectronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	AU,B,61113/90 (640677) (SMITHKLINE BEECHAM PLC) 21 February 1991 (21.02.91). Page 2 lines 2-7, page 3 lines 17-20, claims 1, 2.	1-7, 9-12
X	AU,B,91850/82 (536453) (WELLCOME AUSTRALIA LTD) 24 March 1983 (24.03.83). Page 2a lines 19-23, page 3 lines 19-27, page 8 lines 24-26 and claims.	1-7, 9, 11-12
X	AU,B,91851/82 (546672) (COOPERS ANIMAL HEALTH AUSTRALIA LTD) 24 March 1983 (24.03.83). Page 8 lines 24-26, claims 1, 10.	1-7, 9, 11-12

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "&" document member of the same patent family

Date of the actual completion of the international search 26 April 1994 (24.04.94)	Date of mailing of the international search report 29 April 1994 (29.04.94)
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer  L. TRISTRAM Telephone No. (06) 2832075

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 94/00023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X	AU,B,74018/87 (599383) (COOPERS ANIMAL HEALTH LTD) 10 December 1987 (10.12.87). Page 1A lines 2-5, 22-28, page 4 lines 1-8, page 10 lines 7-12, claim 6.	1-7, 9-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU 94/00023

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.